these questions we develop a reaction based minimal model of the exponentially growing E. coli in a glucose medium.

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Computational Modeling Predicts Phosphatase Oxidation as an Important Axis of Redox Regulation in IL-4 Signaling

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Reactive oxygen species (ROS) are produced following activation of several types of cell surface receptors and can play an important role in modulating cell signaling. How simultaneous oxidative modifications of multiple proteins, sometimes with potentially opposite effects, regulate cell signaling is not well understood at the system level. We are using computational modeling based on quantitative experimental measurements to develop a systemic understanding of redox regulation of cell signaling in the context of the IL-4 signaling pathway. We observe that IL-4 signaling in Jurkat cells is accompanied by transient ROS production, and ROS augment signaling activity as measured by STAT6 phosphorylation. A number of candidate redox-regulated mechanisms exist in the IL-4 pathway that could contribute to the observed outcomes; however, it is technically challenging to directly measure redox modifications of the possibly redox-regulated proteins. To circumvent this issue, we have developed kinetic models of IL-4 signaling that incorporate competing hypotheses regarding redox regulatory mechanisms. With the guidance of measurable experimental data we are using innovative model selection strategies to determine the best candidate models. We have also acquired time course data for processes not directly related to redox regulation, such as transcriptional negative feedback regulation and proteasomal degradation as mechanisms for downregulating IL-4 signaling, that aid model selection and validation. Our results so far indicate that reversible oxidative inhibition of phosphatases and compartmentation of phosphatase activity between subcellular compartments may be the primary redox regulatory mechanisms in IL-4 signaling. These studies will help evolve an understanding of how oxidative modifications of different components of the signaling pathway operate in parallel along with better studied post-translational modification mechanisms of protein regulation to determine the overall dynamics of cell signaling.

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Multi-Finite Buffer Method for Direct Solution of Discrete Chemical Master Equation

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Many biological reaction networks are intrinsically stochastic due to random thermal fluctuations. Stochasticity is significant when the copy number of participating molecular species are small. The discrete Chemical Master Equation (dCME) provides a general framework to study the underlying stochastic processes of biological networks. Although the direct solution of dCME is advantageous over approximation methods such as the Langevin and the Fokker-Planck equations, it is challenging to obtain exact solution to the dCME. The Finite Buffer dCME Method provides an optimal algorithm to enumerate the underlying state space, and has been used to compute the exact solutions of dCME for several problems. In this study, we extend the finite buffer method by introducing multiple buffer queues for more effective construction of the state space and for quantitative control of errors, when buffer sizes are limited. By introducing the concept of open Independent Birth-Death (IBD) units, which are non-intersecting sets of reactions grouped by common synthesis and degradation reactions, we can enumerate the state space optimally and assess errors for each open IBD from the probability of buffer depletion, when the buffer size is limited. We also describe theoretical estimation of the error bound for any given buffer size of an IBD, so its buffer size can be optimized. We demonstrate the effectiveness of our approach in computing time-evolving and steady state probability landscapes, as well as first passage time distribution using the birth-death process, the bistable Schlogl model, the bistable toggle switch model, and the phage lambda lysogenic-lytic switching model as examples. We also compare our results with those using other methods.

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Optimized Energy Dissipation of Minde Oscillator for Symmetric Cell Division

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Prokaryotic cells often utilize a MinCDE oscillatory system to locate the mid-cell location for symmetric cell division. Several diffusion-reaction based models have been developed to explain the occurrence of the sustainable oscillation of Min proteins from pole to pole, and extensive efforts have been devoted to understanding the patterns of oscillation and the precision of the designated mid-cell location. However, how this highly dissipative yet vital biological oscillation is driven by energy-bearing molecules is left uninvestigated. We address this fundamental question by studying the MinCDE oscillator in *Escherichia coli*. We assess the oscillator's performance of spatially differentiating mid-cell region from the rest of cell body, and further relate this quantified performance to the amount of dissipated energy as well as the stage of cell growth. Unlike the two adaptive reaction networks (Negative-Feedback-Loop and Feedfoward-Loop) whose performances get monotonically improved upon larger energy input, the MinCDE oscillator shows nonmonotonic performance-to-cost relation that depends on the reaction rates and the cell length. Our analysis further indicated that this oscillator operates optimally at cell length around 4 micro-meters and to achieve the best performance, energy is dissipated unevenly through the reaction pathway with the largest dissipation at immobilizing MinD and hydrolyzing ATP. These results present a novel mode of converting biochemical energy into spatiotemporal information in living systems and suggest that the MinCDE oscillator in prokaryotic cells are highly optimized both functionally and energetically to ensure high fitness under natural selection.

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Construction of a Self-Consistent Landscape for Multistable Gene Regulatory Circuits

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Cell fate decisions during embryonic development and tumorigenesis pose a major research challenge in modern developmental and cancer biology. Cell fate decisions between different phenotypes (e.g. epithelial, mesenchymal and epithelial/mesenchymal hybrids) are regulated by multistable gene circuits that give rise to the coexistence of several stable states (phenotypes). Internal and external noise play crucial role in determining the transitions between and the relative stability of the coexisting phenotypes. The deterministic dynamics of these circuits is not derivable from a potential. Yet, motivated by Waddington Epigenetic Landscape, many rely on the notion of effective potential to describe cell fate determination in the presence of noise. Here, we present a construction of a self-consistent landscape (effective potential, W = -ln(probability)), utilizing the Eikonal equation approach (WKB approximation of the corresponding Fokker Planck equation) for the cases of white noise and shot noise. The approach is based on utilizing the method of characteristics in a special way, which is illustrated for the concrete examples of the bistable and tristable double inhibition circuits. We also deviced a numerical method to efficiently calculate the contour of the potential and the optimal path for the transitions from one stable state to another. We tested the method on the bistable and tristable double inhibition circuits, and we showed that the constructed landscape agrees very well with the numerical simulation of the stochastic equations. We expect this method to be valuable to a wide range of multistable gene circuits.

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Multistability in GTPase-Based Decision Circuits

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Cell fate decisions during embryonic development and tumorigenesis pose a major research challenge in modern developmental and cancer biology. Cell fate decisions between different phenotypes are regulated by multistable gene circuits that give rise to the coexistence of several stable states (phenotypes). GTPases are molecular switches, which toggle between GTP-bound active state and GDP-bound inactive state. GTPase-based gene regulatory circuits play a crucial role during embryonic development and tumorigenesis. An archetypal example is the RhoA-Rac1 circuit that regulates cell fate determination between amoeboid and mesenchymal phenotype. Here, we introduced a biologically consistent, yet tractable, theoretical framework to model and investigate GTPase-based gene regulatory circuits. We show that although the modeling approach incorporates the details of GTPase activation/inactivation dynamics (GTP loading and hydrolysis reactions), it yields relatively simple effective circuit models. The efficiency of this new approach is illustrated for the specific case of the Rac1-RhoA mutually inhibitory feedback loop. We found that this simple two components unit can yield, for realistic circuit